Case fatality ratio and mortality rate trends of community-onset *Staphylococcus aureus* bacteraemia

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Abstract

Lethal outcomes can be expressed as a case fatality ratio (CFR) or as a mortality rate per 100 000 population per year (MR). Population surveillance for community-onset methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus* bacteraemia was conducted in Canada, Australia, Sweden and Denmark to evaluate 30-day CFR and MR trends between 2000 and 2008. The CFR was 20.3% (MSSA 20.2%, MRSA 22.3%) and MR was 3.4 (MSSA 3.1, MRSA 0.3) per 100 000 per year. Although MSSA CFR was stable the MSSA MR increased; MRSA CFR decreased while its MR remained low during the study. Community-onset *S. aureus* bacteraemia, particularly MSSA, is associated with major disease burden. This study highlights complementary information provided by evaluating both CFR and MR.

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Death is an important outcome when investigating severe infections. Case fatality ratio (CFR) expressed as the number of deaths per cases is typically reported as the primary indicator of disease severity [1–3]. In comparison, mortality rate (MR) per 100 000 population per year measures death events in a population and is less susceptible to selection bias, thereby potentially being a better marker of disease burden [4]. *Staphylococcus aureus* is an important cause of bacteraemia-associated deaths worldwide. The emergence of methicillin-resistant *S. aureus* (MRSA) has contributed to its changing epidemiology. Despite an annual incidence of 25 per 100 000 and a CFR of 15–25%, there are few MR comparisons [4–9]. In this study, we examined fatal outcomes associated with community-onset *S. aureus* bacteraemia. We explored trends over time and assessed 30-day CFR and MR associated with MSSA and MRSA.

This study utilized a population-based cohort design. Our protocol has been previously published [10]. All community-onset *S. aureus* bacteraemias were identified among residents of eight regions within Australia (Canberra), Canada (Calgary, Victoria and Sherbrooke), Denmark (North Denmark, Copenhagen City and Copenhagen County) and western Sweden between 1 January 2000 and 31 December 2008 [5]. Detailed clinical, microbiological and management information was not available. Thirty-day all-cause death outcome was available for all centres except Victoria where 30-day in-hospital death was used as a surrogate.

All analyses were conducted using Stata 12.1 (StataCorp, College Station, TX, USA). Case fatality ratio was calculated as deaths per cases and expressed as a percentage. The MR was calculated as deaths per 100 000 population per year and was age- and gender-standardized to the European Union 27-country 2007 population [10]. We focused on community-onset disease and a 30-day time frame to better attribute death to *S. aureus* bacteraemia because competing risks (i.e. concurrent active illnesses) can influence outcome. The Cuzick non-parametric test for trend across ordered groups was used to compare trends over time.

During the 9-year study period, 5365 incident cases of community-onset *S. aureus* bacteraemia were identified; 5005 (93.3%) MSSA and 360 (6.7%) MRSA. Overall CFR was 20.2% for MSSA (range, 17.3–22.1% annually) and 22.3% for MRSA (range, 10.7–47.4% annually), as shown in Figs 1 and 2. The CFR decreased for MRSA (p 0.05) but remained stable for MSSA (p 0.81). The overall annual MR was 3.4 (range, 2.7–3.9) per 100 000, and was 3.1 (range, 2.5–3.7) per 100 000 for MSSA and 0.3 (range, 0.1–0.4) per 100 000 for MRSA. Annual MR increased for MSSA (p 0.03) but was similar for MRSA (p 0.42). Age-adjusted MR was higher for male patients for

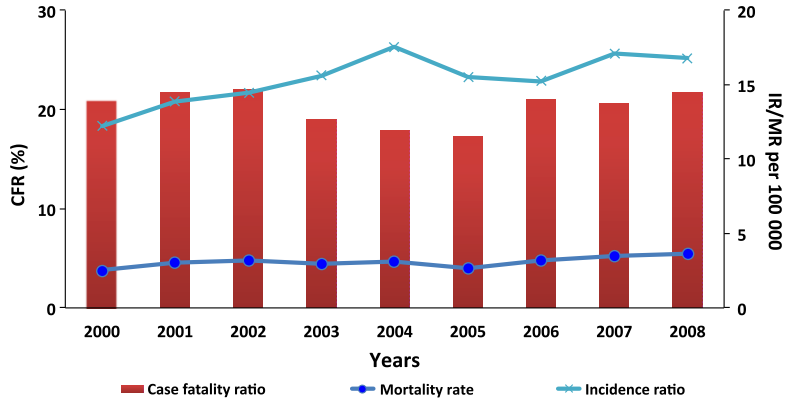

FIG. 1. Overall 30-day case fatality ratio (CFR) and incidence (IR) and mortality rate (MR) per 100 000 population associated with methicillin-sensitive *Staphylococcus aureus* bacteraemia.

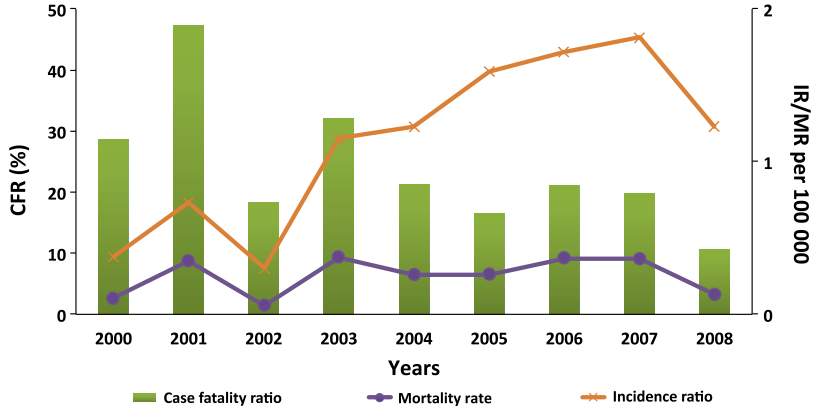

FIG. 2. Overall 30-day case fatality ratio (CFR) and incidence (IR) and mortality rate (MR) per 100 000 population associated with methicillin-resistant *Staphylococcus aureus* bacteraemia.

both MSSA (male, 3.6 per 100 000; female, 2.6 per 100 000) and MRSA (male, 0.3 per 100 000; female, 0.2 per 100 000).

Few population-based studies have reported the CFR or MR associated with community-onset *Staphylococcus aureus* bacteraemia. Studies from the United States (1998), Finland (1995–2001), Australia (1999–2002) and Canada (2000–2006) reported incidence rates of 17, 7, 17 and 12 per 100 000 and associated CFR of 11%, 13%, 18% and 19%, for approximate overall MR of 2, 1, 3 and 2 per 100 000 per year, respectively [11–14]. Other population-based studies have either limited assessment to selected age groups or have not provided data specifically for community-onset disease. Our present study is comparable to these prior studies and overall the body of available information indicates that community-onset *Staphylococcus aureus* bacteraemia is associated with an approximate contemporary incidence of 15 per 100 000 per year, CFR of 20% and MR of 3 per 100 000 per year.

We observed that MSSA MR increased while MSSA CFR was stable and MRSA CFR decreased while MRSA MR remained unchanged (Figs 1 and 2). These findings are largely related to concurrent changes in incidence. In a population-based study, MR can be calculated by multiplying CFR by disease incidence. We have previously demonstrated increasing incidence of community-onset MSSA and MRSA, particularly among the very young and elderly [5]. As MSSA incidence has increased yet CFR remained stable, this can be explained by a proportionate increase in MSSA deaths over the years. Similarly, rising MRSA incidence but decreasing CFR resulted in stable MR. In our opinion CFR is a better marker of disease severity while MR is a better marker of disease burden in a population. This study highlights important differences in and complementary information provided by CFR and MR.

Although this study benefits from its large size and international scope, there are limitations of note. We did not have access to co-morbidities, strain characteristics and adequacy of antibiotic therapy so could not conduct multivariable analysis to control for confounding effects on outcome [15,16]. Given concerns about comparison of crude CFR and MR, individual

centre results were not approved for individual presentations. We observed a relatively low overall rate of MRSA infection and results may not be widely generalizable to populations with higher rates of disease. It is also important to note that MRSA case fatality rates demonstrated high variability (range) in the early years of the study and this was related to small numbers in the early part of the study (9–13 cases per year during 2000–2002 vs. 64–82 cases per year during 2006–2008).

In conclusion, this study highlights the different and complementary information obtained by calculating CFR and MR in the context of incident rates. While much attention has been directed to MRSA disease in recent years, MSSA causes a much greater and increasing burden of disease.

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Author Contributions

ST conducted the primary study analysis and drafted the manuscript. All other authors contributed to study design, acquisition of data, and revision and approval of the final manuscript.

Transparency Declaration

The authors declare no conflicts of interest.

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Appendix

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